A Carbohydrate-Restricted Diet Alters Gut Peptides and Adiposity Signals in Men and Women with Metabolic Syndrome

Matthew R. Hayes, Carla K. Miller, Jan S. Ulbrecht, Joanna L. Mauger, Lynn Parker-Klees, Melissa Davis Gutschall, Diane C. Mitchell, Helen Smiciklas-Wright, and Mihai Covasa

Abstract

Carbohydrate-restricted diets have been shown to enhance satiation- and other homeostatic-signaling pathways controlling food intake and energy balance, which may serve to reduce the incidence of obesity and metabolic syndrome. This study was designed as a correlational, observational investigation of the effects of a carbohydrate-restricted diet on weight loss and body fat reduction and associated changes in circulating leptin, insulin, ghrelin, and cholecystokinin (CCK) concentrations in overweight/obese patients (4 men and 16 women) with metabolic syndrome. Subjects received clinical instruction on the initiation and maintenance of the commercial South Beach Diet, consisting of 2 phases: Phase I (initial 2 wk of the study) and Phase II (remaining 10 wk). Participants showed a decrease (P < 0.05) in body weight (93.5 ± 3.6 kg vs. 89.3 ± 3.4 kg), BMI (33.9 ± 1.3 kg/m² vs. 32.0 ± 1.3 kg/m²), waist circumference (112.8 ± 2.8 cm vs. 107.7 ± 3.0 cm), and total percent body fat (40.2 ± 1.5% vs. 39.2 ± 1.5%) by study completion. Plasma fasting insulin and leptin concentrations decreased significantly from baseline concentrations (139.1 ± 12.2 pmol/L and 44.1 ± 4.5 μg/L, respectively) by the end of Phase I (98.6 ± 2.6 pmol/L and 33.3 ± 4.1 μg/L, respectively). Plasma fasting ghrelin concentrations significantly increased from baseline (836.7 ± 66.7 ng/L) by Phase II (939.9 ± 56.8 ng/L). The postprandial increase in plasma CCK concentrations (difference in plasma CCK concentrations from fasting to postprandial) after Phase I (2.4 ± 0.3 pmol/L) and Phase II (2.5 ± 0.4 pmol/L) was significantly greater than the postprandial increase at baseline (1.1 ± 0.5 pmol/L). Collectively, these results suggest that in patients with metabolic syndrome, improved adiposity signaling and increased postprandial CCK concentrations may act together as a possible compensatory control mechanism to maintain low intakes and facilitate weight loss, despite an increase in fasting ghrelin concentrations and subjective measures of hunger. J. Nutr. 137: 1944–1950, 2007.

Introduction

Interest in carbohydrate-restricted diets in the treatment of obesity has recently increased, because controlled clinical trials have demonstrated that carbohydrate-restricted diets are particularly effective in promoting weight loss in obese adults (1,2). The reason for this effect is not completely understood, but one possibility is that a carbohydrate-restricted diet leads to considerable changes in satiation- and other homeostatic-signaling pathways that control food intake and energy balance (3–6). Although control of food intake and energy balance are governed by the neuronal interactions of a wide variety of gastrointestinal mechanosensory signals (e.g. gut peptides, neurotransmitters, and adiposity signals), a select group of humoral signals are often considered key participants in the control of energy balance. Energy restriction causes a rapid initial reduction in circulating concentrations of the adiposity hormones leptin and insulin that becomes exacerbated with continuous loss of adiposity (7,8). These adiposity hormones communicate to the central nervous system (CNS) the amount of total body adiposity and available energy status, thereby changing the efficacy of satiation signals to terminate a meal. In addition, altered hypothalamic activation by leptin and insulin induces a number of downstream mono- and polysynaptic responses, which simultaneously promote an increase in energy expenditure.

One mechanism by which leptin and insulin reduce food intake is through their interactions with short-term satiation signals such as the intestinally derived gut peptide, cholecystokinin (CCK). When very small amounts of leptin or insulin are

1 Supported in part by NIH grant M01 RR 10732.
* To whom correspondence should be addressed. E-mail: mzc13@psu.edu.
infused directly into the CNS, they greatly enhance the ability of CCK to reduce food intake and, conversely, when leptin or insulin signal in the CNS is reduced, CCK is less efficacious (9–12). Like insulin, long-term elevations in leptin, due to increased adiposity stores in an obese state, can lead to resistance in leptin signaling and deficits in the ability of these adiposity hormones to neuronally affect body weight regulation (13,14). Thus, dietary treatments aimed at body weight reduction may serve to normalize leptin and insulin signaling, presumably restoring the CNS control of energy balance.

In addition to CCK, various other short-term meal controlling signals also work in concert with leptin to control energy balance. The meal-initiating peptide, ghrelin, an endogenous ligand for the growth hormone secretagogue receptor, is one such signal. Ghrelin, an acylated peptide secreted primarily by the stomach (15,16), has been shown to rapidly stimulate food intake in both laboratory animals (17,18) and humans (19) when exogenously administered. Concurrent with a decrease in circulating leptin, plasma ghrelin concentrations increase following weight loss from an energy-restricted diet (20). This reduction in hypothalamic leptin signaling and subsequent increase in ghrelin is thought to elicit a robust increase in appetite.

It is known that each macronutrient present in the diet can affect these body weight signaling pathways differently. For example, Burton-Freeman et al. (21) have shown that meals higher in fat and fiber result in greater feelings of satiety and postprandial rise in CCK than high-carbohydrate, low-fiber meals. Therefore, differing macronutrient compositions of a diet have been shown to significantly alter satiation signaling (3,22,23), circulating energy fuels (24–26), and body composition (24,25,27); dietary modifications involving both reductions in total daily energy intake and alterations in macronutrient composition are appealing strategies for combating obesity and subsequent comorbidities. In particular, the metabolic syndrome, associated with abdominal obesity and insulin resistance, increases health concern for overweight/obese individuals due to its characterized risk factors (28) associated with the development of cardiovascular disease and type 2 diabetes mellitus (29).

The current study was designed as a correlational, observational investigation to assess changes in circulating leptin, insulin, ghrelin, and CCK concentrations following maintenance of a carbohydrate-restricted diet (elevated in protein and mono-unsaturated fatty acids) and its subsequent effects on weight and body fat in overweight/obese patients with metabolic syndrome. Changes in subjective measures of appetite (hunger and fullness) were also examined.

Methods

Subjects. Subjects were eligible for the study if they were >21 y of age and had ≥3 of the following criteria: waist circumference >102 cm in men or >88 cm in women; HDL cholesterol <40 mg/dL (1.02 mmol/L) in men or <50 mg/dL (1.29 mmol/L) in women; triglycerides ≥150 mg/dL (1.69 mmol/L); blood pressure ≥130/85 mm Hg; and/or fasting blood glucose ≥110 mg/dL (6.1 mmol/L) (28). Subjects were excluded from the study if they were diagnosed with diabetes mellitus, currently following a commercial weight reduction program, used oral or parenteral corticosteroids or hormone replacement therapy, required hemodialysis, were pregnant or lactating, or planned on becoming pregnant. The study was approved by The Pennsylvania State University Institutional Review Board. Anthropometric and metabolic outcomes in subjects with metabolic syndrome were reported previously (30).

Nutritional intervention. The diet employed in this study was similar to the South Beach Diet (31) and consisted of 2 phases: Phase I lasted for the initial 2 wk of the study and Phase II ran for the remaining duration (10 additional wk). Phase I of the diet was very low in carbohydrates (10% of energy) with 62% of energy from fat and 28% of energy from protein. Phase II included 43% of energy from fat, 30% of energy from protein, and 27% of energy from carbohydrate.

Subjects met individually with a dietitian for a 60-min session to receive instructions for Phase I of the diet. Two weeks later, they met for an additional 30-min session for instruction in Phase II of the diet. Subjects received printed material regarding the diet that emphasized foods high in protein and monounsaturated fat but low in saturated fats. They were encouraged to eat 3 meals and 2 snacks/day and to avoid extreme hunger. Low-fat cheese, vegetables, or nuts were suggested as possible snack foods. Specific energy restrictions were not given, but subjects were encouraged to pay attention to feelings of satiety and to refrain from eating once satisfied (30).

Data collection. Data collection occurred during 4 visits to the clinic. The first was a screening visit to determine if subjects met metabolic syndrome criteria and were otherwise in good health. Visit 2 (i.e. baseline) occurred immediately before initiation of Phase I. Visit 3 occurred 2 wk later following completion of Phase I and just before subjects began Phase II of the diet. The final data collection (visit 4) occurred 3 mo from baseline after the subjects had been on Phase II for ~10–11 wk.

Anthropometric measure, physical activity, and dietary intake. These measures have been presented elsewhere where methods are fully described (30). Briefly, body weight and waist circumference were assessed at each study visit. Whole body composition was evaluated at baseline and at the end of the study using dual-energy X-ray absorptiometry (model QDR 4500 Elite, Hologic). Body weight and waist circumference were measured (according to NHANES III protocol) at 0800 on each visit following an overnight fast (12 h). A 7-d physical activity recall interview was used to assess energy expenditure (32).

For each data collection period, subjects' dietary intake was assessed via 3 24-h dietary recalls (2 weekdays and 1 weekend day randomly selected over a 1-wk period) using the Minnesota Nutrition Data System for Research (Nutrition Coordinating Center, University of Minnesota). The interviewers were unaware of the dietary instructions provided and had no further contact with the study subjects.

Visual analogue scales questionnaire, experimental meal, and blood draws. Immediately following the anthropometric measurements, blood was drawn into EDTA tubes. Plasma was separated and stored at ~80°C until analysis. Subjects refrained from drinking alcohol and maintained similar exercise schedules for 24 h preceding testing. Immediately following the blood draw, subjects were asked to rate their hunger, thirst, fullness, nausea, and how much food they desired to eat on 100-mm visual analogue scales (VAS), a validated tool widely used both clinically and experimentally to examine these subjective measures (33–37). For example, hunger was rated on the 100-mm line preceded by the question, “How hungry are you right now?” and anchored on the left by “not at all hungry” and on the right by “extremely hungry.” Other anchors consisted of the phrases “not at all” and “extremely” combined with the adjectives “thirsty,” “full,” and “nauseated.” The anchors for the question about desire to eat were “nothing at all” and “a large amount.”

Following completion of VAS questions, subjects were presented with a preweighed breakfast of known macronutrient and energy composition. All subjects received the same 299.4 total kcal (1,253.6 MJ; 1 kcal = 4.187 kJ) meal and 20 fluid oz (600 mL) of chilled water at each visit throughout the study (at baseline, upon completion of Phase I, and upon completion of Phase II). The food composition of the breakfast meal was based on South Beach Diet breakfast recipes [31]; Table 1] and was designed to approximate a late Phase II breakfast by incorporating fruits and whole-grain bread without substantial energy contribution. It should be noted, however, that the macronutrient composition of the test meal was not identical to the daily recommended macronutrient composition, because the proportion of fat and protein was maintained at a relatively low level to minimize a dramatic increase in postprandial

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CCK concentrations. Subjects were asked to consume the entire meal and, immediately following meal completion, they were presented with the same 5 VAS questions as before the meal. Two hours later, another blood sample was obtained.

**Hormone assays.** We measured fasting and postprandial (2 h after meal completion) plasma insulin, ghrelin, CCK, and leptin using commercially available RIA kits. The RIA kits used for measurement of insulin, leptin, and ghrelin were obtained from Linco Research. The intra- and interassay CV were as follows: insulin: <4 and <6%, respectively, with a lower and upper detection limit of 2.0 and 200 U/L (13.89 and 1389 pmol/L), respectively; leptin: <5%, with lower and upper detection limits of 0.5 and 100 μg/L (8 μmol/L), respectively; and total ghrelin: <10 and <14.7%, respectively, with a lower and upper detection limit of 93 and 6000 pg/mL (28 and 1802 pmol/L). Aprotinin-treated plasma CCK-octapeptide was measured using an RIA assay (ALPCO Diagnostics). The intra- and interassay CV for the CCK RIA were <5.5 and 13.7%, respectively, with a lower and upper detection limit of 0.3 and 25 pmol/L, respectively. For all hormone assays, plasma samples from a single subject, at each visit, and for both fasting and postprandial blood draws were analyzed in duplicate in a single assay. Plasma triglycerides and total, HDL, and LDL cholesterol were analyzed by Quest Diagnostics using enzymatic procedures (Corporate HQ). We assessed fasting blood glucose after a finger prick using a glucometer (One Touch Ultra, LifeScan).

**Statistical analyses.** One-way repeated measures ANOVA was used to assess the within-subject impact of the diet on hormones, VAS questionnaires, anthropometric measures, and dietary recall outcome variables across study visits. Significant differences among means were analyzed by Student-Newman-Keuls method for planned comparisons between treatment visits (baseline, Phase I, and Phase II), with \( P < 0.05 \) considered significant. When significant differences were found for hormone concentrations, we conducted regression analyses to determine the independent effects of body weight change and/or change in macronutrient intake on the outcomes. All analyses were made using PC-SAS (version 8.02, SAS Institute). Values reported are means ±SEM unless noted otherwise.

## Results
A total of 108 people were screened by telephone for study eligibility, 59 were eligible to complete the screening visit based on the likelihood of having metabolic syndrome, and 37 agreed to complete that visit. Twenty-four people met the clinical criteria for the metabolic syndrome and were enrolled in the study (4 men and 16 women), 20 of whom completed all data collection visits. Subjects were Caucasian (80% were female). They were (mean ±SD) 47.5 ± 7.2 y old and reported 9.7 ± 6.8 previous attempts at weight reduction.

**Anthropometric measures, physical activity, and dietary intake.** Subjects’ body weight (\( P < 0.001 \)), BMI (\( P < 0.001 \)), waist circumference (\( P < 0.01 \)), and percent body fat (\( P < 0.001 \)) were reduced from baseline values at the end of Phase I and Phase II of the diet (Table 2). Body weight, BMI, and waist circumference were lower after Phase II than after Phase I (\( P < 0.05 \)). However, fasting blood glucose and plasma HDL and LDL cholesterol concentrations did not change during the study. There was also no change in physical activity recall scores or prescribed medications throughout the study (data not shown).

Analysis of the dietary recall data showed that energy intake decreased from baseline to Phase I (\( P < 0.05 \)) with no further

## Table 1
<table>
<thead>
<tr>
<th>Variable</th>
<th>Weight</th>
<th>Energy</th>
<th>Carbohydrate</th>
<th>Protein</th>
<th>Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>g</td>
<td>kcal(1 kcal = 4.187 kJ)</td>
<td>g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scrambled egg, 1 large</td>
<td>60</td>
<td>79.2</td>
<td>1.5</td>
<td>6.5</td>
<td>5.1</td>
</tr>
<tr>
<td>Fresh mushrooms, ~1 Tbsp</td>
<td>5</td>
<td>1.1</td>
<td>0.2</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Whole-wheat bread, 1 slice</td>
<td>25</td>
<td>61.5</td>
<td>11.5</td>
<td>2.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Nonfat plain yogurt, 4 oz</td>
<td>114</td>
<td>83.5</td>
<td>8.7</td>
<td>6.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Blueberries, frozen, 1 cup</td>
<td>155</td>
<td>79.1</td>
<td>18.9</td>
<td>0.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Decaf coffee/tea, 8 fluid oz</td>
<td>237</td>
<td>5.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat-free half and half, 1 Tbsp</td>
<td>15</td>
<td>10.0</td>
<td>1.5</td>
<td>0.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>299.4</td>
<td>42.3</td>
<td>16.6</td>
<td>7.4</td>
<td></td>
</tr>
</tbody>
</table>

1 Values are means ±SEM, n = 20. Means in a row without a common letter differ, \( P < 0.05 \).
changes occurring during Phase II of the diet (Table 3). While subjects did not meet the exact dietary prescriptions for the percentage of energy from the macronutrients (30), the percent of energy from carbohydrates decreased from baseline during Phase I of the diet ($P < 0.05$) and then increased during Phase II ($P < 0.05$) but did not return to baseline. Energy intake from protein increased from baseline to Phase I ($P < 0.05$) and decreased during Phase II compared to Phase I ($P < 0.05$) but also did not return to baseline levels. Percent of energy from total fat and from saturated fat and monounsaturated fatty acids increased significantly from baseline to Phase I of the diet, then decreased during Phase II and returned to baseline levels.

**Hormone assays and VAS questionnaires.** Fasting plasma insulin concentrations were reduced from baseline after Phase I of the diet ($P < 0.001$) but not after Phase II (Fig. 1A). The reduction in fasting plasma insulin concentrations correlated with the increase in the percent of daily energy from protein ($r^2 = 0.27; P < 0.02$) but not with weight loss or changes in percent of daily energy from carbohydrate or fat. Fasting plasma leptin concentrations were also reduced from baseline after Phase I of the diet ($P < 0.001$) and then increased ($P < 0.05$) but remained lower than baseline at the end of Phase II ($P = 0.014$; Fig. 1B). The reduction in fasting plasma leptin concentrations correlated with the reduction in body weight ($r^2 = 0.42; P < 0.01$) but not with alterations in percent of daily energy from carbohydrate, fat, and protein. Fasting plasma ghrelin concentrations were not different from baseline during Phase I of the diet but were greater at the end of Phase II than at baseline ($P = 0.04$) or at the end of Phase I ($P = 0.03$; Fig. 1C). The increase in fasting plasma ghrelin concentrations correlated with the reduction in body weight ($r^2 = 0.20; P < 0.05$) but not with changes in percent of daily energy from carbohydrate, fat, or protein.

Postprandial plasma insulin and ghrelin concentrations did not differ in treatment visits or from within-visit fasting concentrations. However, postprandial plasma leptin concentrations during Phase I were reduced from baseline ($P < 0.001$) but did not differ from within-visit fasting concentrations (data not shown). The postprandial increased plasma CCK concentrations at the end of Phases I and II was greater than the postprandial rise at the baseline visit ($P < 0.05$; Fig. 1D). The increased postprandial rise in plasma CCK concentrations correlated with the increase in percent of daily energy from protein ($r^2 = 0.07; P < 0.05$) but not with weight loss or changes in percent of daily energy from carbohydrate or fat.

Compared to baseline fasting VAS hunger scores, subjects reported higher fasting hunger scores during Phase I of the diet ($P = 0.036$) and further increased hunger scores during Phase II ($P < 0.001$ and $P = 0.048$ from baseline and Phase I, respectively; Fig. 2). The increased fasting VAS hunger scores correlated with the increased fasting plasma ghrelin concentrations ($r^2 = 0.86; P < 0.0001$). At each phase, fasting hunger scores were higher than postprandial hunger scores ($P < 0.001$). Fasting VAS scores of thirst, fullness, nausea, and how much food subjects desired to eat did not differ among treatment visits. At no time throughout the study did subjects report feelings of nausea above a VAS score of 10.2 ± 3.8 mm.

**Discussion**

The results of this study demonstrate that initiation and maintenance on a carbohydrate-restricted diet (31) led to significant reductions in daily food intake, body weight, and total body adiposity that were associated with changes in circulating adiposity (leptin and insulin) and gut (ghrelin and CCK) hormones. Specifically, following initiation and maintenance on this diet, fasting concentrations of leptin and insulin decreased, whereas fasting ghrelin and postprandial CCK concentrations increased. Subjects also reported an increase in subjective hunger scores. However, despite the reduced fasting leptin and insulin, increased subjective fasting hunger scores, and elevated ghrelin, subjects did not report increased daily energy intakes and could adhere to robust shifts in macronutrient composition in their diet. One possible explanation for this may be due to the elimination of leptin and insulin resistance and, consequently, an improvement in CNS leptin and insulin signaling controlling for energy balance. Additionally, the postprandial CCK level was significantly higher compared to baseline, suggesting an increase in satiation signaling and possible compensatory mechanisms resulting in reduced daily energy intakes, thus facilitating weight loss.

Although previous studies conducted in laboratory animals have shown that the ability of acute leptin administration to inhibit food intake is reduced following high fat feeding (38,39), it is not clear whether this effect was due to dietary fat or increased energy content (38). Current findings would suggest that, at least in patients with metabolic syndrome, maintenance on a carbohydrate-restricted diet (elevated in protein and fatty acids) reduces fasting leptin concentrations, body weight, and total adiposity without subsequent increased daily energy intakes.

**TABLE 3** Reported energy and nutrient intake based on 3 24-h dietary recalls at each study visit

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Baseline</th>
<th>Phase I</th>
<th>Phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy, kcal/d (1 kcal = 4.187 kJ)</td>
<td>2079.3 ± 196.2a</td>
<td>1421.7 ± 111.5b</td>
<td>1322.8 ± 105.9b</td>
</tr>
<tr>
<td>Protein</td>
<td>81.7 ± 6.9</td>
<td>16.4 ± 3.2a</td>
<td>96.3 ± 6.1</td>
</tr>
<tr>
<td>Total fat</td>
<td>86.2 ± 9.5</td>
<td>36.3 ± 6.2a</td>
<td>74.6 ± 6.7</td>
</tr>
<tr>
<td>Saturated fat</td>
<td>29.2 ± 3.4</td>
<td>12.3 ± 2.7a</td>
<td>23.7 ± 2.1</td>
</tr>
<tr>
<td>Polyunsaturated fat</td>
<td>18.4 ± 10.5</td>
<td>7.6 ± 2.6ab</td>
<td>15.3 ± 2.1</td>
</tr>
<tr>
<td>Monounsaturated fat</td>
<td>32.1 ± 3.5</td>
<td>13.6 ± 2.5c</td>
<td>29.2 ± 2.6</td>
</tr>
<tr>
<td>Total carbohydrate</td>
<td>241.8 ± 23.6</td>
<td>46.8 ± 7.4a</td>
<td>93.2 ± 12.0</td>
</tr>
<tr>
<td>Added sugar, g/1000 kcal</td>
<td>32.7 ± 3.0a</td>
<td>13.9 ± 2.7b</td>
<td>16.4 ± 13.1b</td>
</tr>
<tr>
<td>Fiber, g/1000 kcal</td>
<td>8.0 ± 0.4</td>
<td>9.1 ± 0.7</td>
<td>9.0 ± 0.7</td>
</tr>
</tbody>
</table>

1 Values are means ± SEM, $n = 20$. Statistical analysis was conducted on percent of daily energy intake for each nutrient. Means in a row without a common letter differ, $P < 0.05$.  

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Together, this suggests that maintenance on a carbohydrate-restricted diet associated with weight loss normalizes leptin signaling. One interesting finding that might reflect the contribution of the macronutrient composition on fasting insulin and leptin concentrations compared to total daily energy intake comes from the fact that compared to Phase I, fasting concentrations of leptin and insulin both were significantly higher in Phase II. However, it should be noted that Phase II fasting concentrations of insulin did not differ from baseline, and fasting leptin concentrations were still significantly reduced. Energy intake did not differ between Phases I and II, whereas macronutrient composition did. Thus, while total energy intake contributes to fasting levels of adiposity signals, dietary macronutrient composition plays a role in circulating values as well. For example, regression analysis indicated that the increased percent of daily energy from protein correlated with the reduced fasting insulin concentrations. Thus, the transition from a restricted (Phase I) to a less restricted carbohydrate diet (Phase II) may potentially increase circulating concentrations of leptin and insulin in humans with metabolic syndrome.

It has been suggested that hyperinsulinemia and/or insulin resistance suppresses fasting ghrelin concentrations (40–42). A previous report by McLaughlin et al. (42) has shown that plasma ghrelin concentrations are lower in insulin-resistant overweight or obese individuals compared to BMI-matched insulin-sensitive subjects. The findings showing both a reduction in fasting insulin and an increase in fasting ghrelin concentrations by Phase II would suggest that in patients with metabolic syndrome, maintenance on a carbohydrate-restricted diet attenuates insulin resistance-induced reduction in ghrelin concentrations. Thus, fasting ghrelin concentrations at the end of the 3-mo study may reflect a restoration to more normal concentrations. However, controlled examination of this effect using BMI-matched insulin-sensitive subjects still remains to be tested. Therefore, it is plausible that the absence of an increase in ghrelin concentrations at the end of Phase I, despite reduction in fasting insulin, may indicate that subjects still expressed functional insulin resistance. Additionally, the increased subjective reports of hunger were likely associated with the increased ghrelin concentrations despite the fact that ghrelin may have been restored to normal concentrations by study completion. Whether macronutrient composition of the diet alone or energy restriction was causal for the observed improvements in anthropometric measures and associated changes in humoral signals cannot be determined from this study.

The elevation in subjective measures of hunger without a compensatory increased daily energy intake suggests a normalization of meal-cued signaling with possible increased functionality in satiation signaling. This is supported by the fact that the postprandial CCK concentrations were significantly increased following initiation (Phase I) and maintenance (Phase II) on the South Beach Diet compared to baseline responses.
postprandial CCK concentrations following the test meal would most likely be due to increased chronic exposure of the small intestine to protein and fat during maintenance on the South Beach Diet. CCK is released from intestinal endocrine I cells in response to fats and proteins [for review, see (43)]. Intraduodenal infusion of the monounsaturated fatty acid oleate or unhydrolyzed protein increases circulating CCK (44,45) and neuronal signaling in the dorsal vagal complex, a region known to control meal size through the CCK-1 receptor (45–47). Given the relatively increased levels of dietary fat and protein, it is not surprising to see a rise in postprandial CCK compared to the baseline concentrations. Studies in humans (3,21) have shown that postprandial CCK concentrations are elevated following adaptation on a low-carbohydrate/high-fat diet when compared to postprandial CCK concentrations preceding dietary adaptation. The most noticeable difference in postprandial CCK elevations occurred 90 to 120 min following a standard test meal after a 2-wk low-carbohydrate/high-fat dietary adaptation (3). Our current findings support this, because blood draws taken 120 min following test meal completion showed that CCK concentrations increased following the 2-wk maintenance on the carbohydrate-restricted diet and this increase remained significant during the study.

In response to protein preloads, elevated postprandial CCK concentrations correlate with subject measures of satiety but do not affect energy intake (48). Interestingly, daily energy intake is also not altered in response to exogenous CCK-induced suppression of an individual meal (49). Collectively, this supports the notion that although postprandial CCK concentrations contribute to feelings of satiation during a meal, postprandial CCK concentrations alone do not dictate daily energy intake, nor is the control of daily intake dependent solely on CCK signaling. Thus, regulation of energy balance involves complex neuronal communication between various neuroregulatory adiposity (e.g. leptin and insulin) and orexigenic (e.g. ghrelin) signals, as well as within-meal anorectic gut peptides (e.g. CCK). In this study, despite the increased postprandial rise in CCK concentrations following Phases I and II, VAS measurements of satiety did not differ and yet daily intake and body weight were reduced. This further indicates that the observed results are likely the combined consequence of improved adiposity signaling by leptin and insulin, as well as compensatory changes in CCK concentrations to offset the increased fasting ghrelin concentrations and subjective reports of hunger. Furthermore, it may be that CCK’s putative role in controlling daily intake was not due to reducing meal size outside of the laboratory but rather increasing intermeal interval due to elevation in CCK concentrations. Thus, subjects may not have taken frequent snacks but instead spaced out their meal taking in a normalized fashion. One main purpose of this study was to assess the role of the maintenance diet (South Beach diet) on changes in CCK release after a meal. Considering the increased postprandial CCK concentrations, it is tempting to speculate that perhaps the loss of body weight (or body fat) induced compensatory responses that acted to increase food intake and, yet, the macronutrient profile of the maintenance diet acted to enhance postprandial satiety. Thus, the resulting net effect of sustained weight loss may be easier to achieve on a carbohydrate-restricted diet as opposed to a low-fat weight-loss diet. The results of this study are insufficient to confirm these conclusions; however, they have considerable merit. Future studies are needed to ascertain the impact of the South Beach Diet on meal frequency, size, and pattern. Future studies should also consider compliance to recommended dietary intakes. Although study subjects made considerable changes in macronutrient intake, they did not achieve dietary goals. We did not query subjects about barriers to meeting goals. Nor do we know whether more extensive counseling would affect compliance and metabolic outcomes.

In conclusion, our findings demonstrate that a carbohydrate-restricted diet, relatively elevated in monounsaturated fatty acids and protein, was effective in reducing body weight, total body adiposity, blood pressure, and waist circumference in overweight/obese patients with metabolic syndrome. Concurrent with these anthropometric improvements, maintenance on the carbohydrate-restricted diet also led to significant reductions in circulating adiposity signals (leptin and insulin), significantly increased ghrelin concentrations, and significantly increased postprandial rise in CCK concentrations, all without a compensatory increase in daily food intake. Collectively, this suggests improved adiposity signaling in the CNS and increased postprandial rise in CCK concentrations may act together as a possible compensatory control mechanism in maintaining reduced intakes and facilitating weight loss, despite increased fasting ghrelin concentrations and subjective measures of hunger. The effects of a carbohydrate-restricted diet on anthropometric and metabolic parameters and associated changes in signals involved in controlling food intake and energy balance using controlled studies is certainly warranted.

### Literature Cited


